What is claimed is:

1. An automated, fast, continuous flow, multi-dimensional method for (1) selecting based on ligand/target interaction, (2) separating, and (3) obtaining physico-chemical data characteristic of, one or more of ligands in a library of solubilized, structurally distinct candidate ligands, the method comprising the steps of:

A. passing a solution comprising said library through a first column to partition, based on a first physico-chemical property, candidate ligands, or complexes of said ligand bond to a target molecule, thereby to produce, a first exit stream; and

B. passing the exit stream, through a second column to partition, based on a second, different physico-chemical property, candidate ligands, said complexes, to generate a second exit stream comprising a subset of candidate ligands having affinity for said target molecule, wherein at least one of said first and second physico-chemical properties is the affinity of a said candidate ligand for said target molecule.

2. The method of claim 1 comprising the additional steps of sampling an exit stream containing a selected ligand after step B and inserting the sample into a mass spectrometer to determine the charge-to-mass ratio of said ligand or a fragment thereof.

3. The method of claim 1 wherein at least one of said first and second physico-chemical properties is selected from the group consisting of the affinity of a candidate ligand for:

a) a target molecule;

b) reverse phase;

c) an ion exchange surface;

d) a chelation surface;

e) a polysaccharide surface; and

f) a polynucleotide

4. The method of claim 1 wherein at least one of said first and second physico-chemical properties is selected from the group consisting of the affinity of a complex of said candidate ligand and a target molecule for:

a) a second target molecule;

b) reverse phase;

c) an ion exchange surface;

d) a chelation surface;

e) a polysaccharide surface; or

f) a polynucleotide surface.

5. The method of claim 1 wherein at least one of said first and second physico-chemical properties is selected from the group consisting of:

a) the binding constant K_b of a candidate ligand for a target molecule;

b) the on rate component of the binding constant of a candidate ligand for a target molecule; and

c) the off rate component of the binding constant of a candidate ligand for a target molecule.

6. The method of claim 1 comprising the step of conditioning said solvent in said exit stream prior to partioning in said second column.

7. The method of claim 1 wherein the first column comprises an affinity column comprising immobilized first target molecules.

8. The method of claim 7 wherein only candidate ligands which fail to bind to said first target molecules are passed through the second column thereby to eliminate candidate ligands which bind to the first target molecule from subsequent screening.

9. The method of claim 8 wherein candidate ligands which bind to said first target molecules are desorbed from said first column and passed through the second column thereby to eliminate candidate ligands which fail to bind to the first target molecule from subsequent screening.

10. The method of claim 8 wherein said second column comprises an affinity column comprising immobilized second target molecules.

11. The method of Claim 9 wherein said second column comprises an affinity column comprising immobilized second target molecules.

12. The method of claim 1 wherein said first column comprises a size exclusion column and, prior to step A, said library is mixed with a target molecule to form candidate ligand/target molecule complexes.

13. The method of claim 1 wherein said second column is a reverse phase column which captures ligands in the exit stream of said first column.

14. A method of detecting in a heterogeneous sample comprising a multiplicity of candidate ligand species a ligand having a high affinity for a target molecule, the method comprising the steps of:

a) digesting biopolymers to produce oligomeric fragments thereof comprising said ligand species;

b) combining with said ligand species produced in step a) with a target molecule, under conditions which will allow candidate ligands, if present, to bind to the target molecule to form a complex; and

c) separating candidate ligands from said complex.

15. The method of claim 14 wherein one or more biopolymers comprise a known binder to said target molecule, or a derivatized or modified form of said known binder.

16. The method of claim 14 wherein said step b) comprises passing the candidate ligand species over a target molecule immobilized on an affinity column, thereby to immobilize on said column a complex comprising said target molecules and candidate ligands and thereafter eluting ligands from said column.

17. The method of claim 16 comprising the additional steps of: eluting ligands into an accumulator to capture a ligand; and eluting said captured ligand from said accumulator.

18. The method of claim 17 wherein isolated ligand is identified by a process comprising determing the mass-to-charge ratio of ions generated therefrom.

19. The method of claim 14 wherein step a) is effected by, immobilizing one or more digestive enzymes on a column and passing one or more biopolymers to be digested through the column to obtain the said oligomeric fragments.

20. The method of claim 14 wherein step b) comprises mixing the candidate ligand species with said target molecule to form soluble complexes thereof and separating complexes from uncomplexed ligand species on a size exclusion chromatography column.

21. A method of detecting the presence of a ligand having a preselected affinity K for a preselected target molecule in a sample of heterogeneous ligands dissolved in a solvent, the method comprising:

a) loading a column with a known concentration T of target molecules;

b) passing a sample through said column to bind ligands in the sample thereto;

c) thereafter passing through the column a series (n) of column volumes of solvent, wherein n is a number of column volumes between 1 and 10,000;

d) passing a subset KT of the column volumes exiting the column of step c) through a ligand accumulator to immobilize thereon ligands having said preselected affinity K wherein the subset of column volumes kp~KT, and,

e) eluting from the accumulator of step d) said ligands having said affinity K.

22. The method of claim 21 wherein, during step b), the velocity of the sample passing through the column is selected to modulate the on-rate component of the affinity constant of the ligand sought to be detected, wherein increasing the velocity of the sample through the column results in the binding in step b) and elution in step e) of ligands having a larger on-rate.

23. The method of claim 21 wherein, during step c), the velocity of solvent passing through the column is selected to modulate the off-rate component of the affinity constant of the ligand sought to be detected, wherein increasing the velocity of the solvent through the column results in the elution in step e) of ligands having a higher off-rate.

24. The method of claim 21 comprising the step of passing the eluate of step (d) through an interface to a mass spectrometer.

25. The method of claim 21 further comprising the step of independently optimizing the flow rate through the columns of step a) and b), and independently optimizing the flow rate of the eluate to a mass spectrometer for determination of the mass-to-change ratio of a ligand in said eluate.

26. A method for separating mixed ligand species dissolved in a solvent into separate fractions of ligands, each fraction being characterized by a different affinity or range of affinities for a preselected target molecule, the method comprising:

a) passing the mixed ligand species through a column having immobilized thereon target molecules to bind ligands to the column;

b) passing through the column a series of column volumes of solvent;

c) passing at least two subsets of the column volumes of solvent exiting the column of step b) through a ligand accumulator to immobilize thereon ligands characterized by separate ranges of affinity constants; and

d) eluting from the accumulator of step c) said at least two fractions containing ligands characterized by different ranges of affinities.

27. The method of claim 26 further comprising diverting consecutive subsets of the column volumes of solvent exiting the column of step b) to different accumulator columns.

28. A method of assay for rapidly detecting the presence, absence or concentration of an analyte in a sample, said analyte having a known affinity constant K in a preselected solvent for a binding molecule, the method comprising the steps of:

a) providing a matrix comprising a column having loaded therein immobilized binding molecule having the affinity K for the analyte;

b) passing a sample through the matrix to bind analyte to said binding molecule;

c) passing through the matrix a series (n) of column volumes of the solvent, wherein n is a number of column volumes between 1 and 10,000;

d) passing a subset kp of the column volumes exiting the column of step c), which subset contains said analyte, if present, through an analyte accumulator to immobilize thereon analyte having said preselected affinity K, wherein the subset of column volumes kp~KT, wherein T is the concentration of binding molecules in said matrix;

e) eluting analyte present in the accumulator of step d) to produce an eluate; and

f) detecting the absence, presence or concentration of analyte in said eluate.

29. A method of detecting in a heterogeneous sample comprising a multiplicity of ligand species the presence of a ligand having a desired high affinity K for a preselected target molecule when said ligand and said target molecule are present together in preselected solvent conditions, the method comprising:

a) immobilizing a target molecule onto a column;

b) passing the sample through said column under conditions to promote binding of ligands in the sample to the target molecules;

c) thereafter passing through the column a series of column volumes of solvent defining said solvent conditions;

d) passing a subset kp of the column volumes exiting the column of step c) through a ligand accumulator to immobilize thereon ligands having said desired high affinity, and

e) eluting said ligands from the accumulator of step d).

30. The method of claim 29 wherein a ligand eluted in step e) is characterized by a said high affinity K for said target molecule equal approximately to kp/T where T is the concentration of target molecules in said column.

31. A method of detecting, in a heterogeneous sample comprising multiple ligand species at least some of which bind a preselected target molecule with an affinity of at least about 10^4 M^{-1}, the presence of a ligand having a high on-rate, Ko, when said ligand and said target molecule are present together in preselected solvent conditions, the method comprising:

a) immobilizing a target molecule onto a column;

b) providing said heterogeneous sample in a solvent defining said preselected solvent conditions;

c) passing the sample of step b) through said column at a high linear fluid velocity so as to minimize residence time of ligands of said sample in said column thereby to bind selectively high on-rate ligands to said target molecules in preference to other ligands in the sample;

d) thereafter eluting said column to produce an output and identifying said high on-rate ligands.

32. The method of claim 31 comprising the additional step of passing the output of step d) through a ligand accumulator and eluting the accumulator to produce an output rich in said high on-rate ligand.

33. A method for the selective screening of a library of heterogeneous ligands to detect a desired ligand characterized by at least two different preselected binding characteristics to first and second target molecules, said method comprising the steps of:

a) combining a solution of heterogeneous ligands with a first target molecule under conditions such that candidate ligands bind to said first target molecule thereby to form candidate ligand/first target molecule complex;

b) passing the complex of step a), or candidate ligands separated from said complex, through an affinity column containing immobilized second target molecule; and

c) collecting from said column those ligands having the desired binding characteristics.

34. The method of claim 33 wherein one of step a) and step b) is performed by introducing the library to a column having the first target molecule immobilized thereon.

35. The method of claim 33 wherein one of step a) and step b) is performed by introducing the complex and unbound components to a size exclusion column and collecting the complex therefrom.

36. The method of claim 33 further comprising passing solution exiting the column of step b) through an accumulator to immobilize thereon ligands having the desired binding characteristics.

37. An instrument for isolating selected ligands

which have an affinity for and display preferential binding to a preselected target molecule, in amounts sufficient to permit physico-chemical structural characterization thereof,

the instrument comprising structure defining a variable flow path controllable by the user for passing solutions through various paths thereof and, disposed along said flow path:

an inlet for receiving a mixed solution containing at least a multiplicity of different candidate ligands;

a first column, in fluid communication with said inlet, for partitioning candidate ligands, or complexes thereof with a target molecule, on the basis of the varying affinity of said candidate ligands for a target molecule;

a second column, for receiving an output from said first column, for further partitioning ligand species in said output on the basis of interaction with a different target molecule, one of said target molecules comprising said selected target molecule; and

a valve interposed between an outlet of said first column and an inlet of said second column for directing a selected portion of the output of said first column to said second column.

38. The apparatus of claim 37 further comprising at least one additional column for partitioning ligands, or complexes of ligands with a target molecule, passing therethrough, on the basis of interaction with still another different target molecule.

39. The apparatus of claim 38 wherein said at least one additional column is interposed between said first and second columns and the output from said first column passes through said additional column before entering said second column.

40. The apparatus of claim 38 wherein said at least one additional column is disposed after said second column and is adapted to receive at least a portion of an output from said second column.

41. The apparatus of claim 37 further comprising a ligand accumulator connected through a valve to an output of said second column or a said additional column for capturing a subset of ligands characterized by said affinity for and preferential binding to said preselected target molecule.

42. The apparatus of claim 41 wherein said accumulator is a reverse phase chromatography column, which permits chromatographic separation of accumulated ligands.

43. The apparatus of claim 37 further comprising an instrument for determining a physico-chemical structure aspect of a selected ligand exiting a said column or accumulator.

44. The apparatus of claim 43 wherein said means is a mass spectrometer.

45. The apparatus of claim 37 disposed between consecutive columns for conditioning the solvent characteristics of an output stream of an upstream column for partitioning within a downstream column.

46. The apparatus of claim 37 for isolating selected ligands which will bind to target molecules from a first biological source but not to structurally related target molecules from a second biological source, wherein said first unit is an affinity column comprising immobilized target molecules from said second source, said second unit is an affinity column comprising immobilized target molecules from said first source, and said valve directs ligands which do not bind to said first for capture in said second unit.

47. An integrated multi-dimensional system for isolating and for obtaining physico-chemical data characteristic of ligands having an affinity for a preselected target molecule, said system comprising,

structure defining a variable flow path controllable by the user for passing solutions through various paths thereof and, disposed along said flow path:

an affinity column comprising immobilized target molecules;

an accumulator in fluid communication with an output from said affinity column; and

a mass spectrometer for determining the charge-to-mass ratio of ligands eluted from said accumulator.

48. The system of claim 47 further comprising an interface between the accumulator and the mass spectrometer, the interface comprising:

a) a sampler having a predetermined sample volume switchable alternatively to be in fluid communication with an eluate stream of the accumulator and an input of the mass spectrometer; and.

b) a sampler controller for controlling the sampler to first extract a sample from said eluate stream thereby to capture a sample of eluate and thereafter to insert the captured sample into the input of the mass spectrometer.